ORIGINAL ARTICLE

Meningococcal Serogroup ACWYX Conjugate Vaccine in Malian Toddlers

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ABSTRACT

BACKGROUND

Neisseria meningitidis serogroups A, B, C, W, X, and Y cause outbreaks of meningococcal disease. Quadrivalent conjugate vaccines targeting the A, C, W, and Y serogroups are available. A pentavalent vaccine that also includes serogroup X (NmCV-5) is under development.

METHODS

We conducted a phase 2, observer-blinded, randomized, controlled trial involving Malian children 12 to 16 months of age. Participants were assigned in a 2:2:1 ratio to receive nonadjuvanted NmCV-5, alum-adjuvanted NmCV-5, or the quadrivalent vaccine MenACWY-D, administered intramuscularly in two doses 12 weeks apart. Participants were followed for safety for 169 days. Immunogenicity was assessed with an assay for serum bactericidal antibody (SBA) with rabbit complement on days 0, 28, 84, and 112.

RESULTS

A total of 376 participants underwent randomization, with 150 assigned to each NmCV-5 group and 76 to the MenACWY-D group; 362 participants received both doses of vaccine. A total of 1% of the participants in the nonadjuvanted NmCV-5 group, 1% of those in the adjuvanted NmCV-5 group, and 4% of those in the MenACWY-D group reported local solicited adverse events; 6%, 5%, and 7% of the participants, respectively, reported systemic solicited adverse events. An SBA titer of at least 128 was seen in 91 to 100% (for all five serotypes) of the participants in the NmCV-5 groups and in 36 to 99% (excluding serogroup X) of those in the MenACWY-D group at day 84 (before the second dose); the same threshold was met in 99 to 100% (for all five serotypes) of the participants in the NmCV-5 groups and in 92 to 100% (excluding serogroup X) of those in the MenACWY-D group at day 112. Immune responses to the nonadjuvanted and adjuvanted NmCV-5 formulations were similar.

CONCLUSIONS

No safety concerns were identified with two doses of NmCV-5. A single dose of NmCV-5 elicited immune responses that were similar to those observed with two doses of MenACWY-D. Adjuvanted NmCV-5 provided no discernible benefit over nonadjuvanted NmCV-5. (Funded by the U.K. Foreign, Commonwealth, and Development Office; ClinicalTrials.gov number, NCT03295318.)

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Neisseria meningitidis is known to cause outbreaks of meningitis in many parts of the world. The sub-Saharan African meningitis belt, which stretches from Senegal to Ethiopia, has the highest annual incidence of invasive meningococcal disease, with outbreaks occurring on an annual basis and with recurrent large epidemics every 7 to 14 years.[1-3] Among the several serogroups that have been classified on the basis of their polysaccharide capsule structure, six (A, B, C, W, X, and Y) are known to cause most cases of invasive disease. The serogroup distribution varies regionally, with serotypes A, C, and W being the most common in sub-Saharan Africa until recently. A proportional increase in the incidence of serogroup X disease has been reported, with an increase from 3% of 4150 confirmed meningitis cases during the period from 2013 through 2016 to 22% of 1410 cases in 2017, mainly in Burkina Faso, Niger, and Togo.[4,5]

The two serious manifestations of invasive meningococcal disease are meningitis and septicemia, which can be fatal in 50% of cases if untreated. Even when meningococcal disease is treated, mortality is approximately 10%. Among survivors, 10 to 20% have sequelae such as severe permanent brain damage, mental retardation, deafness, epilepsy, and other neurologic disorders.[1]

To tackle the problem of large epidemics of serogroup A disease in the meningitis belt, MenAfriVac, a meningococcal A conjugate vaccine, was developed in a partnership involving the Serum Institute of India, the World Health Organization, and PATH, with funding from the Bill and Melinda Gates Foundation.[6] MenAfriVac has been used extensively in mass immunization campaigns and has virtually eliminated serogroup A disease from the meningitis belt[7,8]; however, other serogroups, such as C, W, and X, continue to be reported.[9-12]

Currently, three A, C, W, and Y meningococcal conjugate vaccines are commercially available (Menactra, Menveo, and Nimenrix)[13]; however, no licensed vaccine includes serogroup X. Therefore, a pentavalent meningococcal conjugate vaccine incorporating the A, C, W, Y, and X serogroups (NmCV-5) was developed by the Serum Institute of India in partnership with PATH. In a phase 1 clinical study involving healthy adults in the United States, two formulations of NmCV-5 (with and without adjuvant) showed an acceptable safety profile and encouraging immunogenicity.[14] Given these results, we conducted a phase 2 trial involving Malian toddlers to assess the safety and immunogenicity of this vaccine in this age group, to determine the need for an adjuvant in the formulation, and to determine whether one or two doses would be needed to elicit immune responses.

Methods

Trial Design and Oversight

We conducted a phase 2 randomized, controlled, observer-blinded, single-center trial involving healthy Malian children 12 to 16 months of age. The trial was designated to be observer-blinded, which meant that the vaccine preparation and administration in masked syringes were handled by site staff who were aware of the trial group assignments but did not participate in any of the clinical trial evaluations. The parents or legal guardians of the participants, the site staff involved in the evaluation of trial end points, and the laboratory staff who performed the immunogenicity assays were unaware of which trial vaccine was administered to each participant. Full details of the trial design are provided in the protocol, available with the full text of this article at NEJM.org.

The trial was approved by the research ethics committee of the Faculté de Médecine, de Pharmacie et d'Odonto-Stomatologie, Bamako, Mali, and by the institutional review board of the University of Maryland, Baltimore. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. Full written informed consent was provided by each participant's parent or legal guardian before enrollment. An independent data and safety monitoring board was constituted to assess the safety of the vaccines during the trial.

Trial Population

Children 12 to 16 months of age were recruited from the urban Bamako area. Children were excluded from the trial if they had a history of any meningococcal vaccination or disease or had had any intimate contact with a person with meningococcal infection in the previous 60 days. Other major exclusion criteria were a history of hypersensitivity to any of the vaccine compo-

nents, any clinically significant disorders, immune deficiency, malnutrition, known hepatitis B or C, human immunodeficiency virus infection, or malaria at the time of vaccination.

TRIAL VACCINES

NmCV-5 is a lyophilized powder containing meningococcal serogroup A and X polysaccharides conjugated to tetanus toxoid and meningococcal serogroup C, W, and Y polysaccharides conjugated to recombinant CRM197 (cross-reactive material 197, a nontoxic mutant of diphtheria toxin) protein. The vaccine was reconstituted with either normal saline (nonadjuvanted formulation) or with normal saline containing aluminum phosphate (adjuvanted formulation) just before administration. After reconstitution, each 0.5-ml dose of NmCV-5 contained 5 μg each of the meningococcal serogroup A, C, W, Y, and X polysaccharides. The licensed MenACWY-D conjugate vaccine (Menactra, Sanofi Pasteur) was supplied as a single 0.5-ml dose that contained 4 μg each of the meningococcal serogroup A, C, W, and Y polysaccharides conjugated to diphtheria toxoid.

OBJECTIVES AND PROCEDURES

The primary objective was to assess severe reactogenicity (i.e., grade 3 local and systemic solicited adverse events) of the nonadjuvanted and adjuvanted formulations of NmCV-5 as compared with MenACWY-D. The secondary objectives were to assess safety further (all other grades of solicited adverse events, unsolicited adverse events, adverse events that led to withdrawal from the trial, and serious adverse events) and to assess the immunogenicity of the two NmCV-5 formulations as compared with MenACWY-D.

The participants visited the trial clinic on day 0 (baseline) and on days 7, 28, 84, 91, 112, and 168. On day 0, eligible participants were randomly assigned, in a 2:2:1 ratio, to receive two doses of nonadjuvanted NmCV-5, adjuvanted NmCV-5, or MenACWY-D. Two doses of each vaccine were to be administered intramuscularly, with the first injection on day 0 and the second on day 84.

Local and systemic solicited adverse events occurring within 7 days after each vaccination were assessed daily by site staff and recorded in the home-visit worksheets. Data on unsolicited adverse events with an onset within 28 days after each vaccination were collected weekly by site staff during home and site visits. Data on serious adverse events and adverse events that led to withdrawal from the trial were collected during the entire trial period.

Solicited local adverse events included tenderness and swelling or induration at the injection site. Solicited systemic adverse events included irritability, drowsiness, decreased eating, vomiting, and fever. Secondary safety end points were mild and moderate grades of solicited adverse events with an onset during the 7 days after each vaccination, unsolicited adverse events with an onset during the 28 days after each vaccination, and serious adverse events and adverse events leading to premature withdrawal from the trial. The severity of all adverse events was graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1.

For the assessment of secondary immunogenicity end points, approximately 5 ml of blood was obtained from the participant just before each vaccination (on days 0 and 84) and at 28 days after each vaccination (on days 28 and 112). The serum samples were tested with an assay for the serum bactericidal antibody (SBA) with baby rabbit complement at the central Public Health England laboratory (Manchester, United Kingdom) to measure functional antibodies against meningococcal serogroups A, C, W, Y, and X.[15]

STATISTICAL ANALYSIS

We calculated that the enrollment of 375 participants (150 participants in each NmCV-5 group and 75 participants in the MenACWY-D group) would provide the trial with 80% power to detect a difference of 15.4 percentage points in the incidence of severe solicited adverse events between each NmCV-5 group and the MenACWY-D group, with the use of Fisher's exact test at a significance level of 0.05, under the assumption that the incidence of severe reactions would be 5% in the MenACWY-D group and that 10% of the participants would withdraw from the trial. The percentage of participants who had at least one severe solicited adverse event within 7 days after any trial vaccination (in the periods of days 0 to 6 and days 84 to 90) was the primary safety end point to be compared between each NmCV-5 group and the MenACWY-D control group in a descriptive manner. The safety population included all the participants who were enrolled, received at least one dose of trial vaccine, and

had any safety data available. The between-group differences in the percentages were provided, along with two-sided 95% confidence intervals obtained by the Miettinen and Nurminen method[16]; similar analyses were conducted for all applicable secondary end points.

The comparisons of immunogenicity between the NmCV-5 groups and the MenACWY-D group and between the nonadjuvanted NmCV-5 group and the adjuvanted NmCV-5 group were performed with the use of a noninferiority method. Noninferiority was assessed by examining whether the lower limit of the 95% confidence interval for the between-group difference in percentages was above −10 percentage points (a commonly accepted noninferiority margin) for each serogroup (A, C, W, Y, and X). The immunogenicity analysis was performed in the per-protocol population, which included all the participants who correctly received their assigned trial vaccine with no major protocol deviations that were determined to potentially interfere with the immunogenicity assessment and who provided, at least at one time point after vaccination, a serum sample that could be evaluated. A supportive analysis of immunogenicity was also conducted in the full analysis population, which included all the participants who underwent randomization, received at least one dose of trial vaccine, and provided, at least at one time point after vaccination, a serum sample that could be evaluated; this analysis was conducted according to randomly assigned trial group.

The immunogenicity analyses in each group included the geometric mean titer (GMT) of SBA for each meningococcal serogroup (A, C, W, Y, and X) at day 0 (prevaccination baseline value) and at days 28, 84, and 112. The percentages of participants with SBA titers of at least 128 at each of these trial days were calculated, as were the percentages of participants who had an increase of at least 4 times the baseline SBA titers (i.e., among participants with a prevaccination SBA titer of <8, a postvaccination titer of ≥32; among participants with a prevaccination SBA titer of ≥8, a postvaccination titer of ≥4 times the prevaccination titer) that were obtained at days 28 and 112 (i.e., 4 weeks after each vaccination).

The exact two-sided 95% confidence intervals for the percentages were calculated by means of the Clopper–Pearson method for all applicable end points. The GMTs were provided, with two-sided 95% confidence intervals, by exponentiation of the corresponding means of $\log_2$-transformed SBA titers and their 95% confidence intervals. Missing values were treated as missing at random. A post hoc sensitivity analysis was performed to examine the effect of missing data. The last-observation-carried-forward and worst-case methods were used to impute missing data for the primary end point. For immunogenicity end points, the mean value and worst-case methods were used for imputation. All the statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

TRIAL POPULATION

The trial was conducted from November 2017 through August 2018. Among the 379 children who underwent screening, 2 had a screening failure and 1 had early withdrawal of informed consent. Therefore, 376 participants underwent randomization; 150 children were assigned to each of the NmCV-5 groups and 76 to the MenACWY-D group. Informed consent was withdrawn before the receipt of the first dose for 1 participant who had been assigned to the nonadjuvanted NmCV-5 group. The remaining 375 participants received the first dose of trial vaccine, 362 received the second dose, and 360 completed the trial. Among the participants who received any dose of vaccine, 15 discontinued or withdrew from the trial; 3 discontinuations were due to death, 10 due to protocol deviations, 1 due to withdrawal of informed consent, and 1 due to travel. At the end of the trial, there were 375 participants in the safety population and 360 in the per-protocol population (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

All the participants were Black African, and there was a slight preponderance of male participants in each trial group (range, 51 to 55%). Overall, the mean age of the participants was 12.1 months, and the median age was 12.0 months. The distributions of length (mean [±SD], 72.9±2.7 cm) and weight (mean, 8.8±1.1 kg) were similar across all three groups.

SAFETY RESULTS

No immediate adverse events were reported within 30 minutes after vaccination. None of the participants had any severe solicited adverse events. After the first vaccine dose, 1 of 149

participants (1%) in the nonadjuvanted NmCV-5 group, 2 of 150 (1%) in the adjuvanted NmCV-5 group, and 3 of 76 (4%) in the MenACWY-D group had at least one local solicited adverse event. No local solicited adverse events were reported after the second dose.

Overall, 6% of the participants in the nonadjuvanted NmCV-5 group, 5% of those in the adjuvanted NmCV-5 group, and 7% of those in the MenACWY-D group reported systemic solicited adverse events. Systemic solicited adverse events were reported after the first dose in 8 of 149 participants (5%) in the nonadjuvanted NmCV-5 group, in 6 of 150 (4%) in the adjuvanted NmCV-5 group, and in 3 of 76 (4%) in the MenACWY-D group; systemic solicited adverse events after the second dose were reported in 1 of 144 participants (1%), in 2 of 145 (1%), and in 2 of 73 (3%), respectively. Only fever and vomiting were reported as solicited adverse events after the second dose. Other than two events of fever of moderate severity (one each in the nonadjuvanted NmCV-5 group and the adjuvanted NmCV-5 group), all the solicited adverse events were mild in severity (Table S1).

During the 28 days after receipt of the first dose, 37 of 149 participants (25%) in the nonadjuvanted NmCV-5 group, 39 of 150 (26%) in the adjuvanted NmCV-5 group, and 23 of 76 (30%) in the MenACWY-D group reported 48, 46, and 28 unsolicited adverse events, respectively. None of these 122 adverse events, other than 2 events of diarrhea in participants in the nonadjuvanted NmCV-5 group, were assessed by the investigator as being related to a trial vaccine.

During the 28 days after receipt of the second dose, 23 of 144 participants (16%) in the nonadjuvanted NmCV-5 group, 17 of 145 (12%) in the adjuvanted NmCV-5 group, and 16 of 73 (22%) in the MenACWY-D group reported 24, 17, and 17 unsolicited adverse events, respectively. None of these 58 adverse events were assessed by the investigator as being related to a trial vaccine.

Almost all the unsolicited adverse events that were reported during the trial were respiratory tract infections, gastroenteritis, or diarrhea. All the unsolicited adverse events were mild or moderate in severity, and all resolved without any sequelae (Table S2).

Three serious adverse events, one in each group, occurred during the trial, and all led to death. These events were pneumonia (in the nonadjuvanted NmCV-5 group), *Escherichia coli* sepsis (in the adjuvanted NmCV-5 group), and second-degree burns (in the MenACWY-D group). All three serious adverse events were assessed by the investigator as being unrelated to a trial vaccine (Table S3).

IMMUNOGENICITY RESULTS

The SBA GMTs for each meningococcal serogroup in the per-protocol population are presented in Figure 1 and Table S4. The GMTs at baseline (day 0) were low (≤4.4) across all three trial groups. At all subsequent time points and for all serogroups, the GMTs were higher in both the nonadjuvanted NmCV-5 group and the adjuvanted NmCV-5 group than in the MenACWY-D group.

At 84 days after receipt of the first dose, the GMTs were proportionally reduced from those at 28 days after receipt of the first dose for all serogroups in both the NmCV-5 groups and the MenACWY-D group. GMTs were higher at 28 days after receipt of the first dose of either formulation of NmCV-5 than they were 28 days after receipt of the second dose of MenACWY-D, despite an increase in the GMTs after the second dose of MenACWY-D.

At baseline, for all five serogroups, 15% or less of the participants in each of the three groups had an SBA titer of at least 128 (Table 1). At 28 days after receipt of the first dose, 97% or more of the participants (lowest lower boundary of the 95% confidence interval [CI], 93.0) in the two NmCV-5 groups had SBA titers of at least 128 against all five serogroups, whereas in the MenACWY-D group, SBA titers of at least 128 in at least 90% of participants were limited to serogroups A and W. The response in the MenACWY-D group against serogroup C was 54% (95% CI, 42 to 66), whereas it was 99% (95% CI, 95 to >99) in the nonadjuvanted NmCV-5 group.

Just before the receipt of the second dose (at day 84), at least 91% of the participants in the two NmCV-5 groups still had SBA titers of at least 128 against all five serogroups. In the MenACWY-D group, this threshold (≥128) was maintained in more than 90% of participants only for serogroup A; for serogroup C, 36% of the participants (95% CI, 25 to 48) had an SBA titer of at least 128.

At 28 days after receipt of the second dose (day 112), at least 99% of the participants in the two NmCV-5 groups had an SBA titer of at least 128 against all five serogroups. In the MenACWY-D

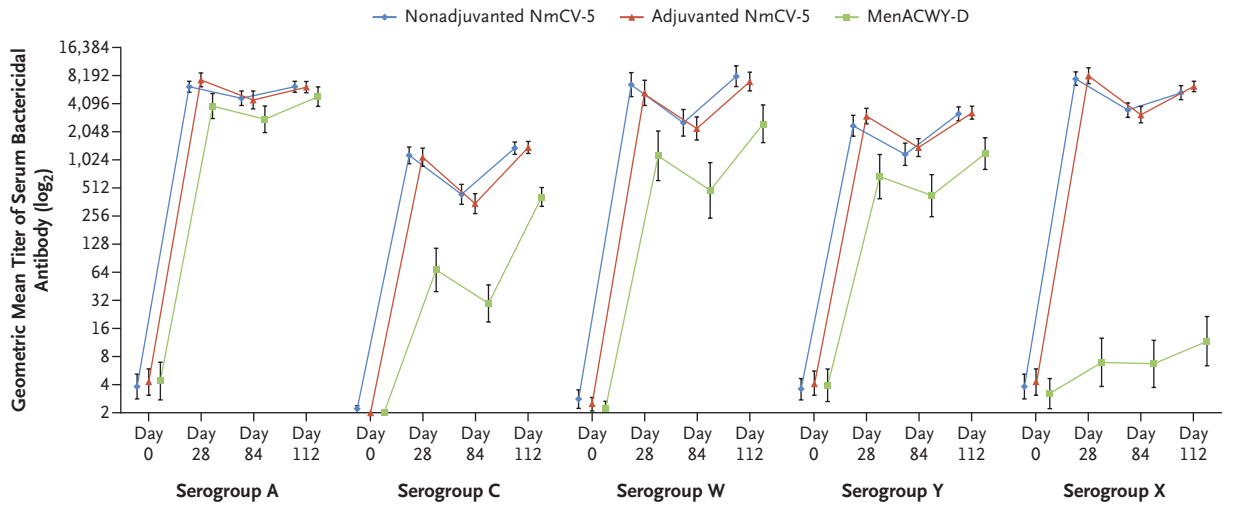

Figure 1. Geometric Mean Titers of Serum Bactericidal Antibody, According to Meningococcal Serogroup (Per-Protocol Population).

Shown are the geometric mean titers and 95% confidence intervals (I bars) of the serum bactericidal antibody with baby rabbit complement that were observed in participants who received nonadjuvanted NmCV-5, adjuvanted NmCV-5, or MenACWY-D at baseline (day 0), at 28 days and 84 days after receipt of the first dose (days 28 and 84), and at 28 days after receipt of the second dose (day 112). The per-protocol population included all the participants who correctly received their assigned trial vaccine with no major protocol deviations that were determined to potentially interfere with the immunogenicity assessment of the trial vaccines and who provided, at least at one time point after vaccination, a serum sample that could be evaluated.

group, this threshold was met in at least 91% of the participants for serogroups A, C, W, and Y.

At 28 days after receipt of the first vaccine dose, 97% or more of the participants (lowest lower boundary of the 95% CI, 93) in each NmCV-5 group had a minimum increase of 4 times the baseline SBA titers against all five serogroups, whereas in the MenACWY-D group a minimum increase of 4 times the baseline SBA titers was observed in at least 90% of the participants only for serogroups A and W and was observed in 69% of the participants (95% CI, 58 to 80) for serogroup C (Table 2). At the day 112 visit, which was scheduled to be 28 days after receipt of the second vaccine dose, more than 98% of the participants in all three groups had a minimum increase of 4 times the baseline SBA titers against all the serogroups included in the respective vaccines.

There were no notable differences between the nonadjuvanted NmCV-5 group and the adjuvanted NmCV-5 group for any serogroup and at any time point with regard to the percentage of participants with SBA titers of at least 128 (Table 1) or the percentage of participants with a minimum increase of 4 times the baseline SBA titers (Table 2) after each trial vaccination. For the percentage of participants with SBA titers of at least 128 for all five serogroups on days 28, 84, and 112, the lowest lower boundary of the 95% confidence intervals for the between-group differences (between each of the NmCV-5 groups and the MenACWY-D group) was −3 percentage points. For the percentage of participants who had an increase of at least 4 times the baseline titer for all five serogroups on days 28 and 112, the lowest lower boundary of the 95% confidence intervals for the between-group differences was −4 percentage points. The immunogenicity results in the full analysis population (369 participants) did not differ substantially from those in the per-protocol population (360 participants). The primary safety end-point results and immunogenicity results from the post hoc sensitivity analysis were similar to those observed in the planned analysis.

DISCUSSION

This phase 2 trial involving Malian toddlers was conducted to assess the safety and immunogenicity of nonadjuvanted and adjuvanted formula-

Table 1. Participants with Serum Bactericidal Antibody Titers of at Least 128 at Days 0, 28, 84, and 112 (Per-Protocol Population).*

Trial Day and Serogroup	Nonadjuvanted NmCV-5 (N=144)		Adjuvanted NmCV-5 (N=144)		MenACWY-D (N=72)	
	no.	*% (95% CI)*	*no.*	*% (95% CI)*	*no.*	*% (95% CI)*
Day 0						
A	16	11 (6 to 17)	18	12 (8 to 19)	10	14 (7 to 24)
C	2	1 (<1 to 5)	0	0 (0 to 3)	0	0 (0 to 5)
W	8	6 (2 to 11)	5	3 (1 to 8)	2	3 (<1 to 10)
Y	16	11 (6 to 17)	21	15 (9 to 21)	10	14 (7 to 24)
X	15	10 (6 to 17)	12	8 (4 to 14)	6	8 (3 to 17)
Day 28						
A	144	100 (97 to 100)	144	100 (97 to 100)	71	99 (92 to >99)
C	142	99 (95 to >99)	140	97 (93 to 99)	39	54 (42 to 66)
W	142	99 (95 to >99)	141	98 (94 to >99)	65	90 (81 to 96)
Y	140	97 (93 to 99)	143	99 (96 to >99)	64	89 (79 to 95)
X	144	100 (97 to 100)	143	99 (96 to >99)	15	21 (12 to 32)
Day 84						
A	144	100 (97 to 100)	143	99 (96 to >99)	71	99 (92 to >99)
C	133	92 (87 to 96)	131	91 (85 to 95)	26	36 (25 to 48)
W	137	95 (90 to 98)	139	97 (92 to 99)	57	79 (68 to 88)
Y	138	96 (91 to 98)	141	98 (94 to >99)	60	83 (73 to 91)
X	144	100 (97 to 100)	143	99 (96 to >99)	14	19 (11 to 30)
Day 112						
A	144	100 (97 to 100)	144	100 (97 to 100)	72	100 (95 to 100)
C	144	100 (97 to 100)	144	100 (97 to 100)	68	94 (86 to 98)
W	144	100 (97 to 100)	144	100 (97 to 100)	69	96 (88 to 99)
Y	144	100 (97 to 100)	144	100 (97 to 100)	66	92 (83 to 97)
X	143	99 (96 to >99)	144	100 (97 to 100)	22	31 (20 to 43)

* The titers of serum bactericidal antibody with rabbit complement were assessed at baseline (day 0), at 28 days and 84 days after receipt of the first dose (days 28 and 84), and 28 days after receipt of the second dose (day 112). The per-protocol population included all the participants who correctly received their assigned trial vaccine with no major protocol deviations that were determined to potentially interfere with the immunogenicity assessment and who provided, at least at one time point after vaccination, a serum sample that could be evaluated. For percentage calculations, the denominator is the number of participants with nonmissing values at baseline and postvaccination visits. Data were missing at day 0 for serogroup C in 1 participant in the nonadjuvanted NmCV-5 group and for serogroup W in 1 participant in each NmCV-5 group. CI denotes confidence interval.

tions of NmCV-5 as compared with MenACWY-D. The local reactogenicity profiles of the two NmCV-5 formulations were similar to that of MenACWY-D, and no safety concerns were identified.

The currently licensed polyvalent meningococcal conjugate vaccines for children younger than 2 years of age (Menactra, Menveo, and Nimenrix) do not contain any adjuvant.[17-19] This trial showed that NmCV-5 also does not need an adjuvant, because both formulations elicited similar immune responses to all serogroups at all time points.

MenACWY-D is recommended at a two-dose schedule in children 9 through 23 months of age,[17] and the findings of this trial support this schedule. In contrast, a single dose of NmCV-5 elicited immune responses that were similar to or higher than those observed with the two-dose schedule of MenACWY-D, which indicates that a single dose of NmCV-5 may protect children who

Table 2. Participants with an Increase in Serum Bactericidal Antibody Titers of at Least 4 Times the Baseline Value on Days 28 and 112 (Per-Protocol Population).*

Trial Day and Serogroup	Nonadjuvanted NmCV-5 (N=144)		Adjuvanted NmCV-5 (N=144)		MenACWY-D (N=72)	
	no.	*% (95% CI)*	*no.*	*% (95% CI)*	*no.*	*% (95% CI)*
Day 28						
A	143	99 (96 to >99)	144	100 (97 to 100)	70	97 (90 to >99)
C	141	99 (95 to >99)	141	98 (94 to >99)	50	69 (57 to 80)
W	140	98 (94 to >99)	140	98 (94 to >99)	65	90 (81 to 96)
Y	140	97 (93 to 99)	142	99 (95 to >99)	63	88 (78 to 94)
X	144	100 (97 to 100)	142	99 (95 to >99)	12	17 (9 to 27)
Day 112						
A	143	99 (96 to >99)	144	100 (97 to 100)	71	99 (92 to >99)
C	142	99 (96 to >99)	144	100 (97 to 100)	72	100 (95 to 100)
W	142	99 (96 to >99)	143	100 (97 to 100)	71	99 (92 to >99)
Y	144	100 (97 to 100)	142	99 (95 to >99)	71	99 (92 to >99)
X	143	99 (96 to >99)	143	99 (96 to >99)	19	26 (17 to 38)

* A serum bactericidal antibody titer of at least 4 times the baseline value was defined as follows: a postvaccination titer of at least 32 in participants with a prevaccination titer of less than 8, and a postvaccination titer of at least 4 times the prevaccination titer in participants with a prevaccination titer of 8 or higher. For percentage calculations, the denominator is the number of participants with nonmissing values at baseline and postvaccination visits. Data were missing at days 28 and 112 for serogroup C in 1 participant in the nonadjuvanted NmCV-5 group and for serogroup W in 1 participant in each NmCV-5 group.

receive the vaccine at 12 through 16 months of age. For this age group, Menveo, which is conjugated to CRM197, is recommended at a two-dose schedule and Nimenrix, which is conjugated to tetanus toxoid, at a one-dose schedule.[18,19] Menactra is conjugated to diphtheria toxoid. The single-dose schedule of NmCV-5 is an important consideration in the sub-Saharan African meningitis belt, given considerations of cost and the issues involved in having people return for a second vaccine dose.

NmCV-5 was immunogenic for serogroup X, which is an important observation because there is no currently licensed vaccine against serogroup X. In the past two decades, the incidence of serogroup X disease has increased in the meningitis belt, so an X-containing vaccine has a potential benefit over existing meningococcal conjugate vaccines.[20] The MenACWY-D group also had small increases in responses against serogroup X. Possible explanations include subclinical infections with serogroup X or cross-reactive antibodies.

At 3 months after the first dose (day 84), the percentage of participants in the two NmCV-5 groups who had SBA titers of at least 128 was at least 91% for all five serogroups. By comparison, the same threshold was maintained in 36% of the participants in the MenACWY-D group for serogroup C. The SBA GMTs also remained high 3 months after receipt of the first dose of NmCV-5.

For the percentage of participants with SBA titers of at least 128 for all five serogroups on days 28, 84, and 112, the lower boundaries of the 95% confidence intervals for the between-group differences (between each of the NmCV-5 groups and the MenACWY-D group) were above −10 percentage points. Similar results were observed with regard to the percentage of participants who had an increase of at least 4 times the baseline titer on days 28 and 112. These results suggest the noninferiority of NmCV-5 to MenACWY-D regarding these end points and are in line with the results observed with Menveo, which has also been shown to elicit noninferior or superior immune responses to those of MenACWY-D for all four serogroups included in these two vaccines.[21,22]

At baseline, the percentage of participants with SBA titers of at least 128 was 15% or less for all five serogroups. This finding indicates a decrease in maternal antibodies as well as increasing susceptibility to meningococcal infections by 12 months of age.

Since there was no observed benefit of the adjuvanted formulation over the nonadjuvanted formulation, as well as no notable safety concerns, the nonadjuvanted NmCV-5 formulation was selected for further evaluation. Two phase 3 trials are ongoing to target mass immunization campaigns (in 2-to 29-year-old persons in Gambia and Mali; ClinicalTrials.gov number, NCT03964012) and vaccination in travelers to high-risk regions (with a trial involving 18-to 85-year-old persons in India; NCT04358731).

The results of this trial suggest that NmCV-5 has the potential to affect outbreaks of serotype A, C, W, Y, or X in the sub-Saharan African meningitis belt, a finding that is analogous to the success seen with MenAfriVac. Several studies have shown that expanding the coverage of a monovalent serogroup A to a multivalent vaccine would be cost-effective.[23-25]

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